HELDA
HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

A biodiversity hypothesis

Haahtela, Tari

2019-08

Haahtela , T 2019 , ' A biodiversity hypothesis ' , Allergy : European journal of allergy and clinical immunology , vol. 74 , no. 8 , pp. 1445-1456 . https://doi.org/10.1111/all.13763

http://hdl.handle.net/10138/312960
https://doi.org/10.1111/all.13763

acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

DR. TARI HAAHTELA (Orcid ID : 0000-0003-4757-2156)

Article type : Review

11.2.2019/Draft 2/revised/clean

Invited article

A Biodiversity Hypothesis

Tari Haahtela, Skin and Allergy Hospital, Helsinki University Hospital, University of Helsinki, Finland, email: tari.haahtela@haahtela.fi

Correspondence: Tari Haahtela, Skin and Allergy Hospital, Helsinki University Hospital, University of Helsinki, Finland, email: tari.haahtela@haahtela.fi

Abstract

Biodiversity hypothesis states, that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders. We are protected by two nested layers of biodiversity, microbiota of the outer layer (soil, natural waters, plants, animals) and inner layer (gut, skin, airways). The latter inhabits our body and is colonized from the outer layer. Explosion of human populations along with cultural evolution are profoundly changing our environment and lifestyle. Adaptive immunoregulatory circuits and dynamic homestasis are at stake in the newly emerged urban surroundings. In allergy, and chronic inflammatory disorders in general, exploring the determinants of immunotolerance is the key for prevention and more effective treatment. Loss of immunoprotective factors, derived from nature,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13763
This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

is a new kind of health risk poorly acknowledged until recently. The paradigm change has been implemented in the Finnish allergy programme (2008–2018), which emphasized tolerance instead of avoidance. The first results are promising, as allergy burden has started to reduce. The rapidly urbanizing world is facing serious biodiversity loss with global warming, which are interconnected. Biodiversity hypothesis of health and disease has societal impact, e.g. on city planning, food and energy production and nature conservation. It has also a message for individuals for health and wellbeing: take nature close, to touch, eat, breathe, experience and enjoy. Biodiverse natural environments are dependent on planetary health, which should be a priority also among health professionals. (233 words)

BOX 1. Future Research Perspectives

- Current data of the impact of biodiversity on health and disease are mostly associative, and should aim more to uncover *cause and effect*.
- ”The nature effect” is obvious, but controlled *clinical interventions* to prove symptom reduction or disease prevention, e.g. in allergy are mostly lacking.
- What is an impactful *nature contact* in preventing or treating allergy? Little is known, how the microbiota from the environment transfers to human body via eating, drinking, breathing and touching?
- Mapping of the microbial species and strains never ends, but their *immunopotential mechanisms* and interactions need more attention. That may give incentives for allergy treatment.
- What is essential for human health in the *microbiome*: compositon, diversity or functional capacity?
- A multidisciplinary approach and new methods are needed to explore prerequisites of human health in the context of *planetary health*.

BOX 2. Major Milestone Discoveries

- *The hygiene hypothesis* was first linked to the lack of early childhood infections increasing susceptibility to allergy. The idea has been enlarged to consist of a repertoire of symbiotic micro-organisms and proved essential for the understanding of *immune tolerance*.
- *Human microbiome* consists of all microbial organisms and their genetic content in the human body. The systematic exploration of the human microbiome started little more than 10 years ago.
- *The metapopulation theory* in ecology concerns species and their interactions in naturally or artificially fragmented habitats. It can be used to predict extinction of species. The theory may also be relevant in the microbial world. Metapopulation is a ”population of populations”.

This article is protected by copyright. All rights reserved.

Accepted Article

- *Globalization of health and disease*. The megatrends, urbanization, global warming and biodiversity loss are interconnected and determine human health and safety.

Introduction

The idea that *biodiversity loss leads to immune dysfunction and disease* was introduced in 2011 (1) and supported by observational data of allergy in 2012 (2) (**Figure 1**). By definition, biodiversity is ”the variability among living organisms from all sources, including, inter alia, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part. This includes diversity within species, between species and of ecosystems” (3).

In practice, the key elements of biodiversity include the richness of local and global species; genetic diversity of populations and species; the spatial extent and the state of natural habitats; and the functioning of ecosystems that are essential for mankind to survive. Increasing ecosystem diversity promotes stability through various mechanisms such as functional redundancy, broader utilisation of available resources, weak among-species interactions, and alternative energy channels (4).

At species level, diversity means a lot of species in a given space, but the relative share of each species is small. In a pristine rain forest, we notice a few butterflies, but they all seem to be of different species. In a summer garden we may enjoy rich butterfly life, but at closer look, only a few species can be identified (5). We can readily observe and follow indices of *macrodiversity* like the Living Planet Index (6), but the changes in the *microdiversity* and *genetic diversity* are much more complex to evaluate. For both, however, the same principles seem to prevail. Barn dust is much richer of bacterial species and their strains than urban home dust (7), where only a few species dominate.

Microbial diversity plays a role in health and disease. On normal skin, diversity of the microbiota is high, while exacerbation of e.g. atopic eczema calls invasion of the opportunistic *Staphylococcus aureus* (8) (**Figure 2**). The microbial balance is lost and the clinician prescribes antibiotics to eradicate the pathogen and corticosteroids to suppress the inflammation. Genetic variablity of the species,

This article is protected by copyright. All rights reserved.

Accepted Article

diversity of strains, determines pathogenicity and response to antibiotics, and is under continuous environmental pressure.

Only improved understanding of the causal factors and mechanisms of allergy would allow us to enlarge disease management from treatment of symptoms to effective primary and secondary prevention. This holds also for other chronic noncommunicable diseases (NCDs), although intervening the known risk factors has significantly improved prevention of e.g. cardiovascular conditions (9). Nevertheless, the true causes of the urban NCDs burden are still largely undissolved at the genetic and molecular level.

This paper reviews shortly the allergy epidemic after the Second World War and opens up the so called biodiversity hypothesis linking it to recent observations of environmental changes, human microbiome and immune regulation. Finally, a short prescription *to do* is suggested.

The allergy rise

Asthma and rhinitis, especially if associated with immunoglobulin E (IgE) and aggravated by exposure to allergens, are examples of NCDs, which have been on rise along with urbanization (10–13). Allergic response is expressed in mucous membranes by inflammatory changes characterized by oedema and excess secretion of mucus caused by influx of inflammatory cells like eosinophils. In asthma, disruption of epithelial cell junctions, swelling and thickening of basement membrane are seen even in early stages of disease (14). Clinically, the allergy diagnosis is set by recognizing the typical symptoms, performing skin prick tests or measuring serum IgE antibodies to common allergens. In asthma, prerequisite for diagnosis is also objectively verified airflow variation.

The Finnish and Russian Karelia developed differently after the Second World War as the part of the Russian population continued a small-scale agricultural lifestyle while the Finnish one started to urbanize. The setting gave a unique opportunity to compare occurrence of asthma and allergy across the border (15, 16). Adult cohorts showed that among those born in 1940s, sensitization to pollens and pets was at the same low level in both areas. Thereafter, an almost

This article is protected by copyright. All rights reserved.

Accepted Article

linear increase in the sensitization rate took place among the Finnish younger generations while this did not occur on the Russian side (17) (**Figure 3**). Furthermore, randomly selected schoolchildren from the same areas were first examined in 2003 and again 2010-2012 (18). On both occasions, clinical hay-fever and peanut allergy were almost non-existent in the Russians.

The critical question is why urbanized populations respond with inflammation in contact with natural elements like pollen, food or animals? They seem to be increasingly allergic to nature, the evolutionary home of *Homo sapiens*. The rise was anticipated already in the mid of the nineteenth century along with the industrial revolution (19), but it has really taken off quite recently, after the Second World War.

The allergy gap has appeared in a relatively short period of time, both between the US Amish and Hutterite populations, having the same ancestry (20), and between the genetically close Finnish and Russian Karelia populations. Thus, the main reason cannot lie in the genome wide differences, but rather in change of lifestyle and environment. Also, the higher allergy prevalence in the Finnish Karelia is neither explained by air pollution as the ambient air in Finland is about the cleanest in the world (21) nor by common environmental chemicals (22). The only biologically plausible explanation is changes in immune regulation and its determinants. In Karelia, one indication for this was demonstrated by the CD14 and CC16 polymorphism; the risk alleles for atopic phenotypes in Finland (CD14 C-159T, CC16 A38G), seemed to be protective alleles in Russia (23). This contrasting appearance may be due to epigenetic modifications driven by development of different lifestyle and environment.

Why IgE binds to allergens?

IgE and IgG antibodies are complementary for immune defence. Allergen-specific IgE is directed to protein epitopes different from those recognized by IgG (24). As allergenicity is limited to a small number of protein families, structural features of the IgE binding epitopes may play a role in their allergenicity. IgE has probably evolved much in response to parasitic worms (helminths) and

This article is protected by copyright. All rights reserved.

Accepted Article

arthropods (25). IgE antibody response detects structural features of molecules from these parasites that are less attainable for IgG.

In small children, cow´s milk is a common cause of allergic reactions, and IgE antibody binds effectively to β-Lactoglobulin, the major whey protein. At the epitope level, IgE attaches to the short fragments of polypeptide chain located in the beta strands of the epitopes. These strands cover a flat area on the allergen surface and may mimic similar structures in pathogens like parasites. The surface of a foreign protein may look like a hilly territory, where IgG attaches the hill tops and IgE the roads in between. The beta strands are common in parasites and may share same molecular features with major allergens like birch pollen (Bet v 1) and house dust mite (Der p 1) (26).

In fact, the most common indoor allergen, house dust mite can be regarded as an ectodermal parasite. The common mite in tropics, *Blomia tropicalis*, may even invade the epithelium, and there is a rationale for an IgE-mediated defence in a mite rich environment. Also, a high IgE cross-reactivity between the extracts from mites and the parasite *Ascaris lumbricoides* has been demonstrated as well as the involvement of known allergens like tropomyosin and glutathione-s-tranferases (27). Thus, inappropriate (allergic) response against β-Lactoglobulin may result, at least in part, from epitope structural similarity with potentially harmful proteins.

Development and maintenance of mucosal tolerance seem to depend on environmental exposure to diverse bioparticles and microbiota. In the case of mites, high exposure induces immune regulatory network and peripheral tolerance (28). Efficient interaction between Toll-like receptors with the ligands of microbes and bioparticles enhances normal mucosal function and prevents from allergen-specific Th2 cytokine production (29–31). Importantly, the relationship between allergen dose and response is nonlinear (32, 33). Increase of exposure may turn the harmful immune response to tolerance through various cellular mechanisms, which are employed in allergen specific immunotherapy (34).

This article is protected by copyright. All rights reserved.

Accepted Article

Emerging biodiversity hypothesis

Biodiversity hypothesis states, that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders (35). It enlarges and binds together the three hypotheses of *hygiene* (11, 36, 37), *old friends* (38, 39), *microbial diversity* (40), and *microbial deprivation* (41).

In the Copenhagen birth cohort study, reduced diversity of intestinal microbiota during infancy was associated with increased risk of allergic diseases at school age (42). In populations from South Germany, Austria and Switzerland exposure to farming environment, with rich microbiota, protected from asthma and atopy (43).

In the Finnish Karelia, the characteristics of the natural environment around home was quantified, and the observations supported the biodiversity hypothesis. Healthy teenagers had higher environmental biodiversity with more species of plants around their homes and higher generic diversity of Gram-negative *Gammaproteobacteria* on their skin compared with allergic subjects (2). Also, rich environmental and microbial diversity seemed to increase expression of the cytokine IL-10 in blood mononuclear cells, promoting immune tolerance (2). Furthermore, in a mouse model intradermal application of one specific bacterial genus (*Acinetobacter*), abundant on the skin of healthy teenagers, induced Th1-type gene expression in dendritic cells and keratinocytes and protected against atopic sensitization and lung inflammation (44). The experiment implied, that skin commensals may tune immune responses to environmental allergens. The effect of *Acinetobacter lwoffii* on maternal toll-like receptor signaling and prenatal protection from asthma was already shown by Conrad and coworkers (45).

Next, the environmental effect was explored in 3 studies of children and adolescents in Finland and Estonia (46). The outcome pointed to the same direction: the greener the environment around homes (forest and agricultural land) the smaller was the risk of allergy. This was hardly seen in those under the

This article is protected by copyright. All rights reserved.

Accepted Article

age of 3 years but clearly in teenagers and young adults in whom allergy was readily manifested.

Green space

Recently, results from a large birth cohort in New Zealand suggested that exposure to greenness and vegetation diversity may protect from asthma (47). However, also conflicting results of the allergy risk have been reported (48–50, reviewed in 51). In terms of other non-communicable diseases, the Dutch national health survey indicated less overweight and more physical activity, if the surroundings were more green in terms of vegetation index but not if the evaluation of greenness was based on land-use (52). In South-Africa, depression was associated with less green living space defined by vegetation index (53). Positive effect of green space was particularly evident amongst African individuals. Fox and coworkers did not look for the green space, but observed in 192 countries Alzheimer´s disease associating with greater degree of urbanization and connected this to microbial deprivation (54).

In dogs, urban environment with reduced green space, characterized by land-use around homes, was a risk factor for allergic skin symptoms while bigger family size and contact with farm animals and other pets were allergy protective (55). Interestingly, allergic dogs had more often allergic owners than healthy dogs, which points to common underlying factors of the allergy risk. In another study of comparing the urban and rural dogs, both the living environment and concurrent lifestyle modified skin microbiota and risk of allergic conditions (56). Those dogs with highest risk were living in cities with scarcity of human or other animal contacts while those with the least risk were living in rural areas and had bigger family size and more contacts. Not surprisingly, urban dogs shared their skin microbiota with owners while the microbiota of rural dogs was more diverse enriched by the microbes from natural surroundings. This result accords the contrasts of house dust microbiota in the Finnish and Russian Karelia (57) and urban and rural dust samples (7). Both urban people and dogs are exposed to their own microbiota not enriched by the environmental diversity. Altogether,

This article is protected by copyright. All rights reserved.

Accepted Article

concurrent but still independent associations of environment and lifestyle with microbiota and allergies give hints of causal relationships.

Green space promotes health in several ways (58–61), but assessment of essential determinants is still in infancy. Living environment affects human microbial composition (62), but quantifying green space around homes is only an indirect way of assessing exposure to microbes. How microbes from the environment can colonize the body sites of an individual is poorly understood and documented. When we pick up a blue berry directly from the bush to mouth, how do the microbes travel from the bush to the gut? The relationship of outdoor and indoor microbiota is poorly known and depends also on housing conditions and behaviour of household members. Are the pets running in and out, are the shoes taken off when stepping in? Parajuli and coworkers studied debris deposited on standardized doormats and confirmed that urban built environment reduces transfer of diverse environmental microbiota indoors (63).

The concept of biodiversity can be extended from living species even to biogenic chemicals. In natural environment, we inhale and ingest a wide range of airborne biogenic chemicals in addition to microbiota and particles (64). This coctail is very different in urban environments, but very little is known of its composition or immunogenicity.

The human immune system has been likened to a computer that has genetically inherited mechanisms (programs) but lacks data (65, 66). The database has been provided by natural environments during the co-evolutionary history between humans and immunoregulatory microbes, helmints and parasites. It is a paradox of modern time that collecting and storing *big data* to develop artificial intelligence mounts exponentially, while keeping up the evolutionary database for constant education of immunological intelligence is in danger as humans are increasingly disconnected from natural environments (**Figure 4**).

This article is protected by copyright. All rights reserved.

Accepted Article

Human microbiome

From an ecological point of view, human body is an ecosystem of microbes. It consists of bacteria, archaea, fungi, protozoas and viruses, which inhabit gut, airways, skin and other body parts. Bacteria (encoding close to 3 million genes) are best known, and their amount in the body is about the same as the number of our own cells (encoding about (20 000 genes) (67). They enter the body with food, water, air and via various contacts with the environment and use the body as their habitat. This entity is only complete, when helmints and parasites are added.

Especially the gut microbiome is also called the 'second genome' to which many protective and life-supporting functions have been externalized (68). It orchestrates the cross-talk between our own cells and environmental metagenome. This interplay may be essential in all conditions, where microbial imbalance (dysbiosis), immune dysfunction (poor tolerance) and low-grade inflammation play a role (35).

Two nested layers of biodiversity protect us, consisting of microbes of the environment we live in and those residing in the body (69, 70). The *outer layer* is dependent on the variety of life around us (soil, natural waters, plants, animals). The diversity and composition of the *inner layer* (gut, skin, airways) – the detailed exploration of which started in 2007 (71) – are dependent on colonization from the outer layer (72, 73). To take care of the inner layer, which closely interacts with the immune system, the outer biodiversity needs to be preserved and everyday practices considered. Everything we *eat, drink, inhale and touch* affect online the composition and function of the inner layer which can be readily effected by changes in behaviour (74).

In any given sample, microbial diversity is a measurement that takes into account both species richness (number of different taxa) and evenness (how abundant the taxa are) and is called *alpha diversity* (75). On the other hand, a distance measure between samples that represents the compositional dissimilarity or heterogeneity is called *beta diversity*. The higher the value of the beta diversity the higher the dissimilarity between the samples. In ecology, interpretation is, however, not straightforward (76).

This article is protected by copyright. All rights reserved.

Accepted Article

Diversity and stability of microbiota is mostly promoted in early childhood (77–79), but the interaction of the outer and inner microbial layers never stops. Innate immunity needs constant, life-long exposure with harmless microbes, old friends to create and maintain tolerance (65). Immigrant studies indicate that already in 10 years people from very different environments start to acquire same health risks as the original population (80). Other features of modern life, like massive use of chemicals, pollution and change in household technology, like using laundry detergents, have contributed to the risk, e.g. by increasing dermal and mucosal permeability (81).

Urban environment appears to lack elements necessary for the proper development and maintenance of tolerance against foreign proteins. Skin and nasal microbiome was much richer and more diverse in the Russian youths compared to their Finnish counterpartners (18). The microbiota was associated with contrasting innate immunity gene expression in peripheral blood mononuclear cells, which modified innate inflammatory pathways (82). Smaller asthma risk in US Amish compared to Hutterite farm children was also connected to the innate immunity function (20).

Human observations have been experimented in animal models. For example, mice housed in contact with soil or clean bedding had marked differences in the composition of small intestinal microbiota (83). The microbes aquired from the soil alleviated Th2-driven inflammation, which is a prerequisite for allergic conditions. In another study, mice were protected from airway allergic inflammation by bacterial CpG DNA influencing on lung macrophage expansion (84). Altogether, in mice, commensals promote induction of T regulatory cells (85, 86).

Are the bacterial species important or their diversity? Immunopotential of well known bacteria like *Helicobacter pylori*, *Akkermansia municipula*, *Lactobacillus johnsonii, Acinetobacter lwoffii* and their strains varies markedly. *Bacteroides fragilis* and *Clostridia* promote T cells to secrete IL-10 in the gut (87, 88). A specific strain of *Bifidobacterium* reduces C-reactive protein, a serum inflammatory marker, in patients with psoriasis, ulcerative colitis and chronic fatigue syndrome (89). Bacteria regulate inflammatory processes by several

This article is protected by copyright. All rights reserved.

Accepted Article

mechanisms, e.g. though their cell wall components and metabolites like biogenic amines and toxins (90). Bacterial-derived metabolites such as short-chain fatty acids may even promote epigenetic changes (91).

The role of key species has been recognized, but the effect of microbial diversity on human health is less clear, being sometimes higher, lower, or not different between healthy and diseased individuals (reviewed in 92). Methodological problems also complicate comparisons. The microbial classification based on the traditional 16S ribosomal RNA and its associated amplicon data may be imprecise and too crude to uncover the true microbial diversity. There is a call for new diversity profiles.

Nevertheless, the *function* of the microbial community in question is decisive and is increasingly highlighted in microbiota research, also because metagenomic analyses have become cheaper and more accessible. The human microbiome is also used to predict responses to different environmental inputs like diet (93–95). The ”omic” science (i.e. transcriptomics, epigenomics, metagenomics, metabolomics) together with machine learning show enormous potential to identify critical functional pathways and new hierarchies.

Future research is also built much on ecological approach, which includes determinants such as dispersal, environmental selection and ecological drift, first established for macrodiversity (96).

Altogether, human gut, skin and airway microbiota has a constant influence on immune function and inflammatory responses through a wide range of mechanisms not well explored at the moment.

Case asthma

In general, microbiome studies have mostly focused on the gut and much less to the airways. In not so far back in history, lower airways were regarded sterile, while they seem to be inhabited by a rich bacterial community. However, the impact of any microbial taxa, structure or diversity on asthma is poorly known (reviewed in 97). Environmental microbial exposure is associated with asthma

This article is protected by copyright. All rights reserved.

Accepted Article

risk (98, 99), as is cesaeran section and use of antibiotics during the first years of life (100, 101).

In clinical asthma, a lot of associations between disease and different airway microbial taxa have been suggested, but the results are not consistent (102). The role of viral infections in triggering asthma is agreed upon (103), but again causalities are largely unexplored. Some studies report higher bacterial burden in bronchial brushings or induced sputum in asthma patients compared with controls (104, 105). One study found presence of *Haemophilus parainfluenzae* in bronchial lavage to increase the risk for corticosteroid resistance (106). Sputum fungi have also been investigated, with differing patterns in asthmatics compared with controls (107). The results are usually confounded by treatment. Altogether, the role of the lower airway microbiome in asthma is unsolved.

Circle of causality

(1) *Why is the patient sneezing, coughing and itching, when exposed to an allergen?* Because of an inflammatory defence response, which is inappropriate and excessive, not serving the host to cope with the environment.

(2) *What is the cause of the inflammatory response?* Lack of immune balance. The immune system does not make a proper distinction between danger and non-danger signals but starts to push inflammatory cells to the epithelium to reject e.g. proteins released by the pollen grain. The biological role of eosinophilic granulocytes and their toxic proteins is to neutralize the potentially harmful invader, but now the invader is an innocent bystander like pollen. Eosinophilia is characteristic both to allergic and non-allergic manifestations of asthma and rhinitis, and their numbers often correlate with severity of symptoms. In the non-allergic cases it is not clear, what is the target of the eosinophils. They seem to attack some long-standing mucosal barrier *non-self* like microbial superantigen, which the immune system reads as a constant danger (108). The often chronic course of these conditions refers to an autoimmune-like process (109**)**.

(3) *What is behind the immune imbalance?* Reduced and altered exposure to microbes like commensals and saprophytes, especially in early childhood. We use

This article is protected by copyright. All rights reserved.

Accepted Article

to think allergy as a too active immune response, i.e. *hyper-responsiveness* to bioparticles, but *hyporesponsiveness* is more likely. During the birch pollen season, more transcripts showed modified expression levels in nasal epithelium in healthy compared to allergic students (110). Health is a dynamic and active state, a complex functional balance in the three-dimensional cellular space, where time is the fourth dimension.

(4) *What impoverishes the human microbiome in the gut, skin and respiratory tract?* Loss of contact with biodiverse elements of nature at macro- and microlevel. In gut, the long-term composition and diversity of microbiota is regulated by the diet and nutrient characteristics.

(5) *Finally, what is causing loss of biodiversity, driving modern life and pushing people to the cities?* Population growth with massive exploitation of natural resources. Cultural evolution has revolutionized life conditions all over the world. Urban lifestyle modulates human microbiome and immune response as never before.

This reasoning is an oversimplification as the true process works more like a network or the circle, where the direction of cause and effect is not self-evident (**Figure 5**). We are becoming aware of the central role of environment and lifestyle, also because genome-wide association studies – revealing susceptibility genes – have only explained a minor part of the risk for many NCDs like asthma (111). Epigenetic flexibility under any environmental pressure has gained increasing attention. Altogether, it is obvious, that the human ecosystem is at stake in urban surroundings and faces the challenge of immune adaptation.

Can we change the course?

In Finland (population 5, 5 million), a 10-year national campaign was initiated in 2008 to combat allergic diseases (112–114). The long-term practice of allergen avoidance (both for prevention and treatment) – already taking off in the 1960s – had not reduced the burden or stopped the epidemic, although avoidance is important in managing individual patients with severe symptoms. A public health programme turned avoidance strategy into tolerance strategy, both in terms of

This article is protected by copyright. All rights reserved.

Accepted Article

immunity and psychological attitude. Immunotherapy was also promoted (115). The mid-term results indicate that the programme works as burden of allergy and asthma has started to decrease e.g. in terms of allergy diets, asthma emergencies and overall costs (116).

The promising first results encouraged to expand the idea of endorsing tolerance also for other NCDs. The burden of inflammatory bowel diseases, diabetes, neurological and mental disorders, obesity, and even cancer is cumulating in Finland and elsewhere. *Nature Step* was suggested to stop this development (117). That includes (1) strenghtening connections to nature in everyday life, (2) increasing use of fresh fruits, vegetables and roots, (3) taking features of natural environment to the care of children and elderly, and (4) focusing research on ecosystem services. Probiotics were not actively recommended, but mentioned as an option to support immune balance (118)

In a canine model, providing an intermediate approach between complex human and artificial mouse model, Lehtimäki and coworkers showed recently, that in terms of allergy protection a short-term exposure to environmental microbes via exercise may not be effective enough (56). They suggest that prominent and sustained exposure to environmental microbiotas should be promoted by urban planning and lifestyle changes to support health. The observation has important implications in city life, e.g. to give people opportunities for gardening, cultivating something themselves, and creating small yards for animals and pets. In many European cities like Helsinki, the idea of *green city planning* is taken seriously (119).

On the urban society level, there is no return to the traditional farming life or producing your own food, but it is possible to take natural elements to modern city life in a controlled and safe way. It is a challenge for urban construction, housing, traffic arrangements and for food and energy production (120, 121). Whether this approach will prevent allergy and other NCDs, and slow down increase of health care costs, remains to be proven. Anecdotally, thirty-five years ago urbanization process was reversed in ten Australian aborigins with type II diabetes, who moved back to their traditional country for 7 weeks (122). Their metabolic abnormalities were greatly improved or completely normalized.

This article is protected by copyright. All rights reserved.

Accepted Article

Concluding remarks

The world is urbanizing faster than ever, and United Nations predicts that by 2050 68 % of the of the world population live in cities (123). In 10 years, the world has 43 megacities with more than 10 million inhabitants, most of them in developing regions.

In 2018 World Wildlife Foundation gave an alarming message: wildlife populations show continuous decline, on average by 60 % from 1970 to 2014, and are likely to diminsh further (6). Biodiversity loss may be the most dangerous global megatrend, even exceeding the risks of global warming (123).

For the first time in 2015, UN recognized biodiversity as an essential determinant of human health (125). Long evolutionary history of effective gene-environment interaction has tested mechanisms of immune tolerance and improved survival in natural environments. The relatively sudden appearance of cultural evolution, along with explosion of human populations, has reduced connection to nature and modified lifestyle **(Figure 6).** Nevertheless, cultural evolution *per se* has had a great positive impact in health-care and life expectancy (126). We should not forget the survival game of the human race in natural environments, often hostile and destructive, throughout of our evolutionary past.

The true causes of the post-war allergy epidemic lie deep in immune regulation and its determinants, and microbes are probably the most important effectors (127). Compromised immunity loaded further by heavy air pollution (128) is a dangerous combination exposing huge numbers of people especially in the growing cities of the developing world. Also, global warming prolongs and intensifies pollen seasons, increasing the burden of allergy (129).

CP Wild wrote in 2005, that there is a need for an *exposome* to match the *genome* (130). The exposome refers to total environmental exposures—detrimental and beneficial—that can help predict biological responses (e.g. inflammation) of the organism to environment over time (131). That inclues also the neuroendocrine responses to a variety of stressors cumulating as an *allostatic load* (132). The contact with the biodiversity of natural environment is largely subconscious, and

This article is protected by copyright. All rights reserved.

Accepted Article

in urban setting much of it is lost. The concept of *extinction of experience* describes that loss (133, 134). ”Never been in a forest or seen a wild butterfly, more experience of air conditioned homes, offices, shopping centres and cars”.

Personal connection to nature is vitally important also psychologically (135). In a meta-analysis, health and happiness were associated with nature relatedness (136). Why people love nature? Does this instinct enrich microbiome, improve immune regulation and help to survive? In the urcban setting, people have started isolate themselves from natural environments with both immunological and psychological consequences (137).

A paradigm shift is taking place, when the complex mechanisms of allergy – and NCDs in general – are slowly revealed, and emphasis is turned to immune tolerance (138). This will affect treatment but especially prevention (139, 140).

In research laboratories, big data of our genetic and molecular architecture are produced as never before, but the results should be translated also to practical actions and relevant measures for society and health-care. Medical community is trained to think *patient by patient* and rely on double-blind, placebo-controlled trials. New kind of methods and interventions to test and analyze nature effects are needed. Research on best implementation practices is breaking through. Tackling allergy may show the way to future preventive medicine in close collaboration with other medical specialities, ecologists and public health authorities.

In Finland, a multidisciplinary approach, clinical allergology, microbiology and ecology in front, helped to recognice the slow and silent trends influencing on health and disease in modern society. New kind of initiatives were taken to tackle allergy as a public health problem.

Fifty years ago Rene Dubos gave a famous lecture ”The spaceship earth” at the Meeting of American Academy of Allergy, Asthma & Immunology (141). He anticipated the allergy epidemic and connected the ”altered reactivity” to many of the environmental changes now linked to the biodiversity hypothesis. In 2015, the Lancet Commission defined the concept of *planetary health* as ”the health of human civilization and the state of the natural systems on which it depends”

This article is protected by copyright. All rights reserved.

(142). Human and planetary health go together and depend on biodiversity of life, the exploration of which is a never-ending scientific adventure.

Acknowledgements

Karelia Allergy Study Group has explored the reasons for allergy contrast between the Finnish and Russian Karelia for 20 years. I am grateful for all the support, discussions and evolution of thinking in this group of clinical allergists, ecologists, epidemiologists, geneticians, immunologists, microbiologists, and experts of public health in Finland, Russia and Australia.

Legends for the Figures

Figure 1. The biodiversity hypothesis (1, modified).

Figure 2. Microbiota on healthy and inflamed skin, where microbial diversity and balance is lost (8, modified).

Figure 3. Left panel. Asthma prevalence in the Finnish conscripts 1926–1989 (10). Two lower curves indicate percentages of men exempted at call up medical examination because of asthma (closed circles), and those discharged during course of the service (open circles). **Right panel**. Generational increase in positive allergen-specific IgE levels to birch pollen in the Finnish but not in the Russian Karelia (16, 17, modified). Among older generations, born in the 1940s, the prevalences were at the same low level in Finnish vs. Russian Karelia.

Figure 4. Disconnection of man from the soil. The biological roots of urbanized *Homo sapiens* are cut by asphalt, concrete, and built environment. For example, the use of asphalt in Finland increased 10-fold from 1960 to 1990 (72).

Figure 5. The circle of causality. From the megatrend of urbanization to increase of non-communicable (inflammatory) diseases. Or the other way around, from symptoms to background factors.

Figure 6. Human kind has evolved from natural environments, i.e. from green (soil) and blue (waters) spaces, but is increasingly effected by cultural environment, i.e. gray (urban) space.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

References

1. von Hertzen L, Hanski I, Haahtela T. Natural immunity. Biodiversity loss and inflammatory diseases are two global megatrends that might be related. *EMBOReports* 2011; **12**: 1089–93.
2. Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, Torppa K, Laatikainen T, et al. Environmental biodiversity, human microbiota, and allergy are interrelated. *Proc Natl Acad Sci* U S A. 2012; **109**: 8334–9.
3. Convention on Biological Diversity 1992. www.biodiv.org/convention.
4. McCann KS. The diversity–stability debate. *Nature* 2000; **405**: 228–233.
5. Haahtela T. Allergy is rare where butterflies flourish in a biodiverse environment. *Allergy* 2009; **64**: 1799–803.
6. WWF 2018. Living Planet Report - 2018: Aiming Higher. Grooten, M. and Almond, R.E.A.(Eds). WWF, Gland, Switzerland.
7. Alenius H, Pakarinen J, Saris O, Andersson MA, Leino M, Sirola K, et al. Contrasting Immunological Effects of Two Disparate Dusts - Preliminary Observations. *Int Arch Allergy Immunol* 2009; **149**:81-90.
8. Salava A. Lauerma A. Role of skin microbiome in atopic dermatitis. *Clin Transl Allergy* 2014; **4**:33.
9. Jousilahti P, Laatikainen T, Peltonen M, Borodulin K, Männistö S, Jula A, et al. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observational study. *BMJ* 2016; **352**: i721
10. Haahtela T, Lindholm H, Björksten F, Koskenvuo K, Laitinen LA. Prevalence of asthma in Finnish young men. *Br Med J* 1990;**301**:266–268.
11. Strachan D. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;**55** (Suppl 1):S2–S10S2.
12. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347**: 911–20.
13. Global action plan for the prevention and control of NCDs 2013-2020. Geneve: WHO 2013. http://www.who.int/nmh/events/ncd_action_plan/en/.
14. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Resp Dis* 1985; **131**:599-606.
15. Vartiainen E, Petäys T, Haahtela T, Jousilahti P, Pekkanen J. Allergic diseases, skin prick tests and immunoglobulin E levels in North Karelia, Finland and in Karelia Republic, Russia. *J Allergy Clin Immunol* 2002; **109**: 643-8.
16. Haahtela T, Laatikainen T, Alenius H, Auvinen P, Fyhrquist N, Hanski I, et al. Hunt for the origin of allergy - comparing the Finnish and Russian Karelia. *Clin Exp Allergy* 2015; **45**: 891–901.
17. Laatikainen T, von Hertzen L, Koskinen JP, Mäkelä MJ, Jousilahti P, Kosunen TU, et al. Allergy gap between Finnish and Russian Karelia on increase. *Allergy* 2011; **66**:886-92.
18. Ruokolainen L, Paalanen L, Karkman A, Laatikainen T, von Hertzen L, Vlasoff T, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy* 2017; **47**:665–674.
19. Blackley CH. Experimental researches on the causes and nature of catarrhus aestivus (hay-fever or hay-asthma). Bailliere, Tindall & Cox 1873.
20. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *N Engl J Med* 2016;**375**:411–21.
21. First WHO Global Conference on Air Pollution and Health 2018. https://www.who.int/airpollution/en/

This article is protected by copyright. All rights reserved.

Accepted Article

22. Koskinen JP, Kiviranta H, Vartiainen E, Jousilahti P, Vlasoff T, von Hertzen L, et al. Common environmental chemicals do not explain atopy contrast in the Finnish and Russian Karelia. *Clin Transl Allergy* 2016; **6**:14.
23. Zhang G, Khoo SK, Laatikainen T, Pekkarinen P, Vartiainen E, von Hertzen L,et al. Opposite gene by environment interactions in Karelia for CD14 and CC16 single nucleotide polymorphisms and allergy. *Allergy* 2009; **64**:1333-41.
24. Niemi M, Jylhä S, Laukkanen ML, Söderlund H, Mäkinen-Kiljunen S, Kallio JM, et al. Molecular interactions between a recombinant IgE antibody and the beta-lactoglobulin allergen. *Structure* 2007; **15**:1413-21.
25. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites and the hygiene hypothesis. *Science* 2002; **296**: 490–494.
26. Bielory BP, Mainardi T, Rottem ME. Evolutionary immune response to conserved domains in parasites and aeroallergens. *Allergy Asthma Proc* 2013; **34**: 93–102.
27. Caraballo L, Acevedo N. Allergy in the tropics: the impact of cross-reactivity between mites and ascaris. *Front Biosci* (Elite Ed). 2011; **3**:51–64.
28. von Hertzen L, Haahtela T. Con: House dust mites in atopic diseases: accused for 45 years but not guilty? *Am J Respir Crit Care* Med 2009; **180**: 113-9; discussion 119–120.
29. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by Toll-like receptors is required for intestinal homeostasis. *Cell* 2004;**118**:229–241.
30. Taylor R, Richmond P, Upham J. Toll-like receptor 2 ligands inhibit Th2 responses to mite allergen. *J Allergy Clin Immunol* 2006;**117**:1148–1154.
31. Ege MJ, Bieli C, Frei R, van Strien RT, Riedler J, Ublagger E, et al. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. *J Allergy Clin Immunol* 2006; **117**: 817–23
32. Custovic A, Hallam CL, Simpson BM, Craven M, Simpson A, Woodcock A. Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol* 2001; **108**: 537-9.
33. Tovey ER, Almqvist C, Li Q, Grisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitisation and asthma in a birth cohort. *J Allergy Clin Immunol* 2008; 122: 114–118.
34. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 2014; **133**: 621**–**31.
35. Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, Caraballo L, et al.The biodiversity hypothesis and allergic disease: world allergy organizationposition statement. *World Allergy Organ J* 2013;**6**:3.
36. Gerrard JW, Geddes CA, Reggin PL, Gerrard CD, Horne S: Serum IgE levels in white and metis communities is Saskatchewan. *Ann Allergy* 1976, **37**: 91–100.
37. Strachan DP. Hay fever, hygiene, and household size. *Br Med J* 1989; **299**: 259–60.
38. Rook GAW. Review series of helminths, immune modulation and the hygiene hypothesis: the broader implications of the hygiene hypothesis. *Immunology* 2009; **126**: 3-11.
39. Rook GAW: 99th Dahlem conference on infection, inflammation and chronic inflammatory diseases: Darwinian medicine and the ”hygiene” or ”old friends” hypothesis. *Clin Exp Immunol* 2010; **160**:70–79.
40. Matricardi PM. "99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: controversial aspects of the 'hygiene hypothesis'". *Clin Exp Immunol* 2010; **160**: 98–105.
41. Björkstén B: Diverse microbial exposure - consequences for vaccine development. *Vaccine* 2012; **30**: 4336–40.
42. Bisgaard H, Li N, Bonnelykke K, Chawes BL, Skov T, Paludan-Müller G, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol* 2011; **128**: 646–52. keratinocytes

This article is protected by copyright. All rights reserved.

Accepted Article

43. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al. GABRIELA Transregio 22 Study Group. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011; **364**: 701–9.
44. Fyhrquist N, Ruokolainen L, Suomalainen A, Lehtimäki S, Veckman V, Vendelin J, et al. Acinetobacter species in the skin microbiota protect against allergic sensitization and inflammation. *J Allergy Clin Immunol* 2014; **134**:1301–1309.
45. Conrad ML, Ferstl R, Teich R, Brand S, Blümer N, Yildirim AO, et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe Acinetobacter lwoffii F78. *J Exp Med.* 2009; **206**: 2869–77.
46. Ruokolainen L, von Hertzen L, Fyhrquist N, Laatikainen T, Lehtomäki J, Auvinen P, et al. Green areas around homes reduce atopic sensitization in children. *Allergy* 2015; **70**: 195–202.
47. Donovan GH, Gatziolis D, Longley I, Douwes J. Vegetation diversity protects against childhood asthma: results from a large New Zealand birth cohort. *Nat Plants* 2018; **4**: 358–364.
48. Fuertes E, Markevych I, Bowatte G, et al. Residential greenness is differentially associated with childhood allergic rhinitis and aeroallergen sensitization in seven birth cohorts. *Allergy* 2016; **71**: 1461–1471.
49. Tischer C, Gascon M, Fernández-Somoano A, et al. Urban green and grey space in relation to respiratory health in children. *Eur Respir* J 2017; **49**: 1502112.
50. Fuertes E, Markevych I, von Berg A, et al. Greenness and allergies: evidence of differential associations in two areas in Germany. *J Epidemiol Community Health* 2014; **68**: 787–790.
51. Ruokolainen L. Green living environment protects against allergy, or does it? *Eur Respir J* 2017; **49**:2-4.
52. Klompmaker JO, Hoek G, Bloemsma LD, Gehring U, Strak M, Wijga AH, et al. Green space definition affects associations of green space with overweight and physical activity. *Environ Res* 2018; **160**: 531–540.
53. Tomita A, Vandormael AM, Cuadros D, Di Minin E, Heikinheimo V, Tanser F, et al. Green environment and incident depression in South Africa: a geospatial analysis and mental health implications in a resource-limited setting. *Lancet Planet Health* 2017; **1**: e152-e162.
54. Fox M, Knapp LA, Andrews PW, Fincher C. Hygiene and the world distribution of Alzheimer's disease: epidemiological evidence for a relationship between microbial environment and age-adjusted disease burden. *Evol Med Public Health* 2013, 173–186.
55. Hakanen E, Lehtimäki J, Salmela E, Tiira K, Anturaniemi J, Hielm-Björkman A, et al. Urban environment predisposes dogs and their owners to allergic symptoms. *Sci Rep* 2018; **8**:1585.
56. Lehtimäki J, Sinkko H, Hielm-Björkman A, Salmela E, Tiira K, Laatikainen T, et al. Skin microbiota and allergic symptoms associate with exposure to environmental microbes. *Proc Natl Acad Sci U S A* 2018; **115**: 4897–4902.
57. Pakarinen J, Hyvärinen A, Salkinoja-Salonen M, Laitinen S, Nevalainen A, Mäkelä MJ, et al. Predominance of Gram-positive bacteria in house dust in the low-allergy risk Russian Karelia. *Environ Microbiol* 2008; **10**: 3317–25.
58. Wolch JR, Byrne J, Newell JP. Urban green space, public health, and environmental justice: the challenge of making cities "just green enough". *Landsc Urban Plan* 2014; **125**: 234–244.
59. Gascon M, Vrijheid M, Nieuwenhuijsen MJ. The built environment and child health: an overview of current evidence. *Curr Environ Health Rep* 2016; **3**: 250–257.
60. WHO. Urban Green Spaces and Health – a Review of Evidence. Copenhagen, WHO Regional Office for Europe, 2016.
61. Lanki T, Siponen T, Ojala A, Korpela K, Pennanen A, Tiittanen P, et al. Acute effects of visits to urban green environments on cardiovascular physiology in women: A field experiment. *Environ Res* 2017; **159**: 176–185.

This article is protected by copyright. All rights reserved.

Accepted Article

62. Lehtimäki J, Laatikainen T, Karkman A, von Hertzen L, Haahtela T, Hanski I, Ruokolainen L Nature-oriented daycare diversifies skin microbiota in children-No robust association with allergies. *Pediatr Allergy Immunol* 2018; **29**: 318–321.
63. Parajuli A, Grönroos M, Siter N, Puhakka R, Vari HK, Roslund MI, et al. Urbanization Reduces Transfer of Diverse Environmental Microbiota Indoors. *Front Microbiol* 2018; **9**: 84.
64. Moore MN. Do airborne biogenic chemicals interact with the PI3K/Akt/mTOR cell signalling pathway to benefit human health and wellbeing in rural and coastal environments?
Environ Res 2015; **140**: 65**–**75.
65. Rook GA. Regulation of the immune system by biodiversity from the natural environment: An ecosystem service essential to health. *Proc Natl Acad Sci U S A* 2013; **110**: 18360–67.
66. Rook GA, Rook GA, Raison CL, Lowry CA. Microbial 'old friends', immunoregulation and socio-economic status. *Clin Exp Immunol* 2014; **177**: 1−12.
67. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol* 2016; 14:e1002533.
68. Zhu B, Wang X, Li L. Human gut microbiome: the second genome of human body. *Protein Cell* 2010; **1**: 718**–**25.
69. Hanski I. Micorobes and human well-being. *Ethics Sci Environ Polit* 2014;14:19–25.
70. Ruokolainen L, Lehtimäki J, Karkman A, Haahtela T, von Hertzen L, Fyhrquist N. Holistic view of health: two protective layers of biodiversity. *Ann Zool Fennici* 2017; **54**: 39–49.
71. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The Human Microbiome Project. *Nature* 2007; **449**: 804–10.
72. von Hertzen L, Haahtela T. Disconnection of man and the soil: reason for the asthma and atopy epidemic? *J Allergy Clin Immunol* 2006; **117**: 334–44.
73. von Hertzen L. Plant microbiota: implications for human health. *Br J Nutr 2015*; **114**: 1531-2.
74. Ruokolainen L, Fyhrquist N, Haahtela T. The rich and the poor: environmental biodiversity protecting from allergy. *Curr Opin Allergy Clin Immunol* 2016; **16**: 421-6.
75. Jost L. Partitioning diversity into independent alpha and beta components. *Ecology* 2007; **88**: 2427–39.
76. Anderson M, Crist T, Chase J, Vellend M, Inouye B, Freestone A, et al. Navigating the multiple meanings of beta diversity: a roadmap for the practicing ecologist. *Ecol Lett* 2011;**14**:19–28.
77. Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. *J Allergy Clin Immunol* 2013; **131**: 23–30.
78. Logan AC, Jacka FN, Prescott SL. Immune-microbiota interactions: dysbiosis as a global health issue. *Curr Allergy Asthma Rep* 2016;**16**:1–9.
79. Stokholm J, Blaser MJ, Thorsen J, Rasmussen MA, Waage J, Vinding RK, et al. Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun* 2018; **9**: 141.
80. Yao J, Sbihi H. Prevalence of non-food allergies among non-immigrants, long-time immigrants and recent immigrants in Canada. *Can J Public Health* 2016; **107**: e461-e466.
81. Wang M, Tan G, Eljaszewicz A, Meng Y, Wawrzyniak P, Acharya S, et al. Laundry detergents and detergent residue after rinse directly disrupt tight junction barrier integrity in human bronchial epithelial cells. *J Allergy Clin Immunol* 2018 Nov 27. pii: S0091-6749(18)31665-8.
82. Alenius H, Fyhrquist N, Laatikainen T, Auvinen P, Fortino V, Scala G, et al. Immune-microbiota interaction explaining allergy disparity in Finnish and Russian Karelia. 2019, in press
83. Ottman N, Ruokolainen L, Suomalainen A, Sinkko H, Karisola P, Lehtimäki J, et al. Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse

This article is protected by copyright. All rights reserved.

Accepted Article

model. *J Allergy Clin Immunol* 2018. pii: S0091-6749(18)30934-5. doi: 10.1016/j.jaci.2018.06.024.
84. Sabatel C, Radermecker C, Fievez L, Paulissen G, Chakarov S, Fernandes C, et al. Exposure to Bacterial CpG DNA Protects from Airway Allergic Inflammation by Expanding Regulatory Lung Interstitial Macrophages. *Immunity* 2017; **46**: 457–473.
85. Karimi K, Inman MD, Bienenstock J, Forsythe P. Lactobacillus reuteri-induced regulatory T cells protect against an allergic airway response in mice. *Am J Respir Crit Care Med* 2009; **179**: 186–93.
86. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of clostridia strains from the human microbiota. *Nature* 2013; **500**: 232–6.
87. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci USA* 2010;**107**: 12204−12209
88. Atarashi K, Tanoue T, Oshima K, Suda W et al. Treg induction by a rationally selected mixture of *Clostridia* strains from the human microbiota. *Nature* 2013; **500**: 232−236
89. Groeger D, O'Mahony L, Murphy EF, Bourke JF, Dinan TG, Kiely B, et al. Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes* 2013; **4**:325–39.
90. Sokolowska M, Frei R, Lunjani N, Akdis CA, O'Mahony L. Microbiome and asthma. *Asthma Research and* Practice 2018;**4**:1
91. Woo V, Alenghat T. Host-microbiota interactions: epigenomic regulation. *Curr Opin Immunol* 2017; **44**: 52–60.
92. Karkman A, Lehtimäki J, Ruokolainen L. The ecology of human microbiota: dynamics and diversity in health and disease. *Ann N Y Acad Sci* 2017;**1399**:78**–**92.
93. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized Nutrition by Prediction of Glycemic Responses. *Cell* 2015; **163**: 1079**–**1094.
94. Korem T, Zeevi D, Zmora N, Weissbrod O, Bar N, Lotan-Pompan N, et al. Bread Affects Clinical Parameters and Induces Gut Microbiome-Associated Personal Glycemic Responses. *Cell Metab* 2017; **25**: 1243**–**1253.
95. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 2018; 555: 210**–**215.
96. Hanski I, Ovaskainen O. The metapopulation capacity of a fragmented landscape. *Nature* 2000;**404**:755–758.
97. Aho VT, Pereira PA, Haahtela T, Pawankar R, Auvinen P, Koskinen K. The microbiome of the human lower airways: a next generation sequencing perspective. *World Allergy Organ J* 2015; **8**: 23.
98. von Mutius E, Vercelli D. Farm living: Effects on childhood asthma and allergy. *Nat Rev Immunol* 2010; **10**: 861–8.
99. von Mutius E. Environmental microorganisms and lung health. *Ann Am Thorac Soc* 2014; **11** Suppl 1:13–5.
100. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy* 2008; **38**: 629–33.
101. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: A systematic review. *Pediatrics* 2011; **127**: 1125–38.
102. Huang YJ, Boushey HA. The microbiome and asthma. *Ann Am Thorac Soc* 2014; **11** Suppl 1: 148–51.
103. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. *Curr Opin Allergy Clin Immunol* 2013; **13**: 211–6.
104. Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, Liu J, et al. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *J Allergy Clin Immunol* 2011;**127**:372–81.

This article is protected by copyright. All rights reserved.

Accepted Article

105. Marri PR, Stern DA, Wright AL, Billheimer D, Martinez FD. Asthma associated differences in microbial composition of induced sputum. *J Allergy Clin Immunol* 2013; **131**: 346–52.
106. Goleva E, Jackson LP, Harris JK, Robertson CE, Sutherland ER, Hall CF, et al. The effects of airway microbiome on corticosteroid responsiveness in asthma. *Am J Respir Crit Care Med* 2013; **188**: 1193–201.
107. van Woerden HC, Gregory C, Brown R, Marchesi JR, Hoogendoorn B, Matthews IP. Differences in fungi present in induced sputum samples from asthma patients and non-atopic controls: a community based case control study. *BMC Infect Dis* 2013;**13**:69.
108. Huvenne W, Hellings PW, Bachert C. Role of staphylococcal superantigens in airway disease. *Int Arch Allergy Immunol* 2013; **161**: 304–14.
109. Mukherjee M, Nair P. Autoimmune Responses in Severe Asthma. *Allergy Asthma Immunol Res* 2018; **10**: 428–447.
110. Joenväärä S, Mattila P, Renkonen J, Ma¨ kitie A, Toppila-Salmi S, Lehtonen M et al. Caveolar traffic through nasal epithelium of birch pollen allergen Bet v 1 in allergic patients. *J Allergy Clin Immunol* 2009; **124**: 135–142.
111. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. GABRIEL Consortium. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010; **363**: 1211–1221.
112. Haahtela T, von Hertzen L, Mäkelä M, Hannuksela M; Allergy Programme Working Group. Finnish Allergy Programme 2008-2018--time to act and change the course. *Allergy* 2008; **63**: 634–45.
113. Bousquet J, Bieber T, Fokkens W, Kowalski M, Humbert M, Niggemann B, Simon HU, Cruz AA, Haahtela T. In Allergy, 'A new day has begun'. *Allergy* 2008; **63**: 631-3.
114. von Hertzen LC, Savolainen J, Hannuksela M, Klaukka T, Lauerma A, Mäkelä MJ, et al. Scientific rationale for the Finnish Allergy Programme 2008-2018: emphasis on prevention and endorsing tolerance. *Allergy* 2009; **64**: 678-701.
115. Hoffmann HJ, Valovirta E, Pfaar O, Moingeon P, Schmid JM, Skaarup SH, et al. Novel approaches and perspectives in allergen immunotherapy. *Allergy* 2017; **72**: 1022–1034.
116. Haahtela T, Valovirta E, Bousquet J, Mäkelä M, the Allergy Programme Steering Group. The Finnish Allergy Programme 2008-2018 works. *Eur Respir J* 2017; **49**(6).
117. Haahtela T, Hanski I, von Hertzen L, Jousilahti P, Laatikainen T, Mäkelä M, et al. Nature step to stop non-communicable diseases. *Duodecim* 2017; **133**: 19–26 (in Finnish, abstract in English).
118. Berti C, Agostoni C, Davanzo R, Hyppönen E, Isolauri E, Meltzer HM, et al. Early-life nutritional exposures and lifelong health: immediate and long-lasting impacts of probiotics, vitamin D, and breastfeeding. *Nutr Rev* 2017; **75**: 83**–**97.
119. Russo A, Cirella GT. Modern Compact Cities: How Much Greenery Do We Need? *Int J Environ Res Public Health* 2018;**15**(10).
120. Flandroy L, Poutahidis T, Berg G, Clarke G, Dao MC, Decaestecker E, et al. The impact of human activities and lifestyles on the interlinked microbiota and health of humans and of ecosystems. *Sci Total Environ* 2018; **627**: 1018–1038.
121. Robinson JM, Jacob G. Mills JG, Breed MF. Walking Ecosystems in Microbiome-Inspired Green Infrastructure: An Ecological Perspective on Enhancing Personal and Planetary Health. *Challenges* 2018; **9**: 40; doi:10.3390/challe9020040.
122. O´Dea K. Marked Improvement in Carbohydrate and Lipid Metabolism in Diabetic Australian Aborigines After Temporary Reversion to Traditional Lifestyle. *Diabetes* 1984; **33**: 596**–**603.
123. Population Division of the UN Department of Economic and Social Affairs (UN DESA). The 2018 Revision of World Urbanization Prospects (https://www.un.org/development/desa/publications/2018-revision-of-world-urbanization-prospects.html).
124. Rockström J, Steffen W, Noone K, Persson A, Chapin FS 3rd, Lambin EF, et al. A safe operating space for humanity. *Nature* 2009; **461**: 472–5.

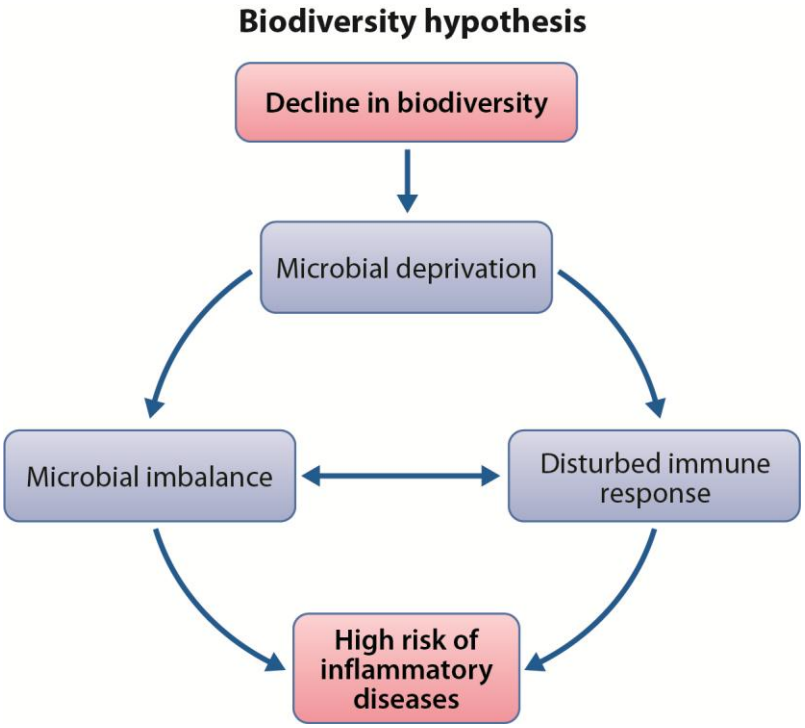
This article is protected by copyright. All rights reserved.

Accepted Article

125. World Health Organization and Secretariat of the Convention on Biological Diversity. Connecting global priorities: biodiversity and human health. A state of knowledge review 2015, p. 1–344.
126. Rosling H, Rosling O, Rosling Rönnlund A. Factfulness: Ten Reasons We're Wrong About The World - And Why Things Are Better Than You Think. Hodder Stoughton 2018.
127. Lee YK, Mazmanian S: Has the microbiota played a critical role in the evolution of the adaptive immune system? *Science* 2010; **330**: 1768–1773.
128. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; **389**: 1907-1918.
129. D'Amato G, Holgate ST, Pawankar R, Ledford DK, Cecchi L, Al-Ahmad M, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. *World Allergy Organ J* 2015; **8**: 25.
130. Wild CP. Complementing the Genome with an "Exposome". The Outstanding Challenge of Environmental Measurement in Molecular Epidemiology. *Cancer Epidemiology, Biomarkers & Prevention* 2005; **14**: 1847–50.
131. Renz H, Holt PG, Inouye M, Logan AC, Prescott SL, Sly PD. An exposome perspective: early-life events and immune development in a changing world. *J Allergy Clin Immunol* 2017; **140**: 24–40.
132. McEwen BS. Brain on stress: how the social environment gets under the skin. *Proc Natl Acad Sci U S A* 2012; **109**(Suppl 2):17180–5.
133. Pyle RM. The extinction of experience. *Horticulture* 1978; **56**: 64–7.
134. Logan AC, Prescott SL, Haahtela T, Katz DL. The importance of the exposome and allostatic load in the planetary health paradigm. *J Physiol Anthropol* 2018; **37**: 15.
135. Silva RA, Rogers K, Buckley TJ. Advancing Environmental Epidemiology to Assess the Beneficial Influence of the Natural Environment on Human Health and Well-Being. *Environ Sci Technol* 2018; **52**: 9545-9555.
136. Capaldi CA, Dopko RL, Zelenski JM. The relationship between nature connectedness and happiness: a meta-analysis. *Front Psychol* 2014; **5**: 976.
137. Le Souëf PN, Goldblatt J, Lynch NR. Evolutionary adaptation of inflammatory immune responses in human beings. *Lancet* 2000; **356**: 242-4.
138. Akdis CA. Therapies for allergic inflammation: refining strategies to induce tolerance. *Nat Med* 2012; **18**: 736–49.
139. von Hertzen L, Beutler B, Bienenstock J, Blaser M, Cani PD, Eriksson J, et al. *Ann Med* 2015; **47**: 218–25.
140. Garn H, Bahn S, Baune BT, Binder EB, Bisgaard H, Chatila TA, et al. Current concepts in chronic inflammatory diseases: Interactions between microbes, cellular metabolism, and inflammation**.** *J Allergy Clin Immunol* 2016; **138**: 47-56.
141. Dubos R. The spaceship earth. *J Allergy* 1969; **44**: 1-9.
142. Whitmee S, Haines A, Beyrer C, Boltz F, Capon AG, de Souza Dias BF, et al. Safeguarding human health in the Anthropocene epoch: report of the Rockefeller Foundation-Lancet Commission on Planetary Health. *Lancet* 2015; **386**: 1973–2028.

This article is protected by copyright. All rights reserved.

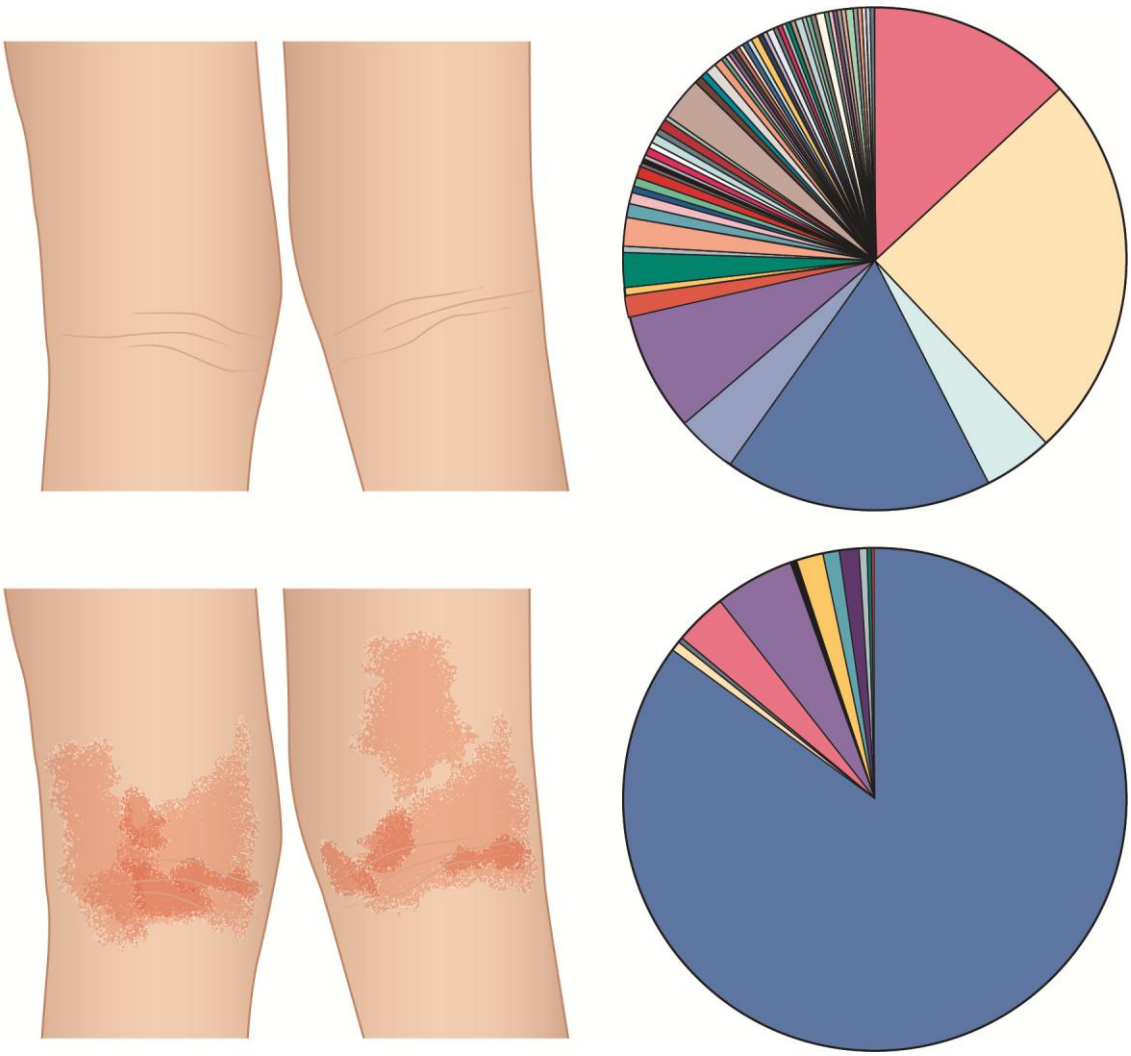
Figure 1. The biodiversity hypothesis (1, modified).



Accepted Article

This article is protected by copyright. All rights reserved.

Figure 2. Microbiota on healthy and inflamed skin, where microbial diversity and balance is lost (8, modified).

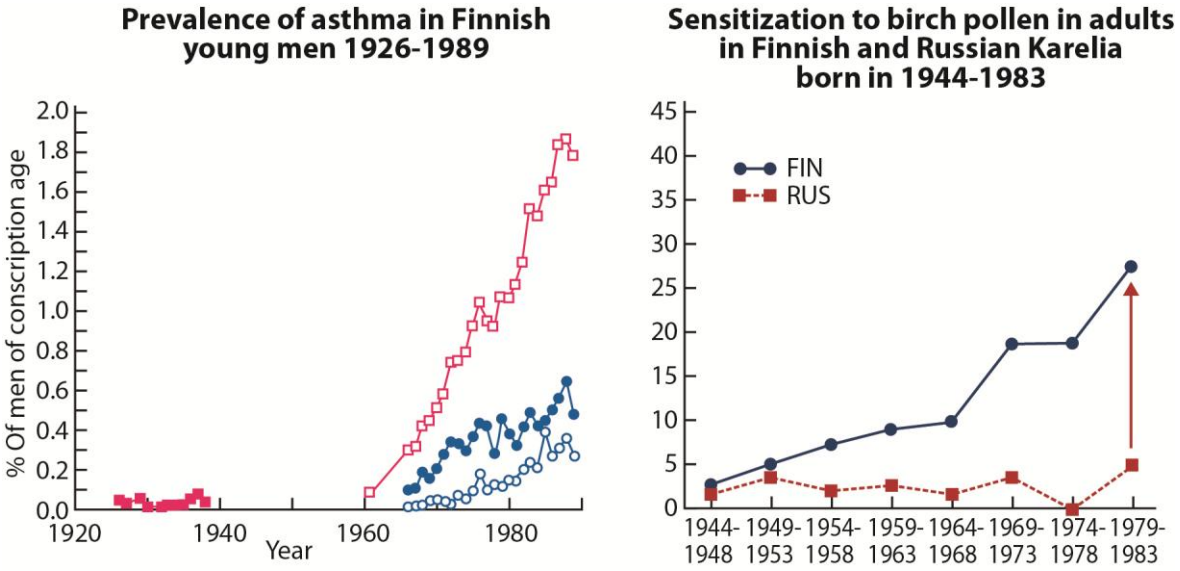


Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Figure 3. Left panel. Asthma prevalence in the Finnish conscripts 1926–1989 (10, modified). Two lower curves indicate percentages of men exempted at call up medical examination because of asthma (closed circles), and those discharged during course of the service (open circles). **Right panel**. Generational increase in positive allergen-specific IgE levels to birch pollen in the Finnish but not in the Russian Karelia (16, 17, modified). Among older generations, born in the 1940s, the prevalences were at the same low level in Finnish vs. Russian Karelia.



This article is protected by copyright. All rights reserved.

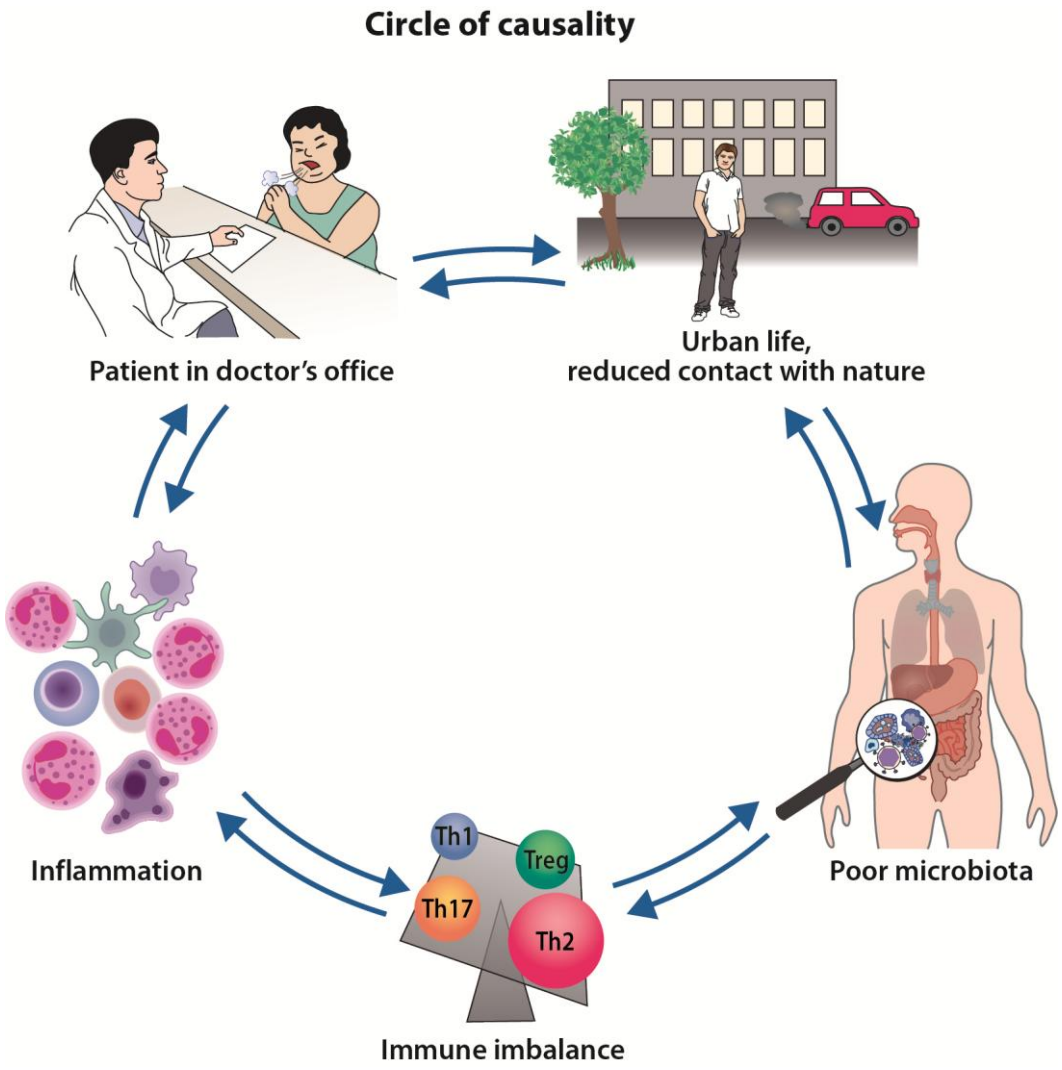
Accepted Article

Figure 4. Disconnection of man from the soil. The biological roots of urbanized *Homo sapiens* are cut by asphalt, concrete, and built environment. For example, the use of asphalt in Finland increased 10-fold from 1960 to 1990 (72).

This article is protected by copyright. All rights reserved.

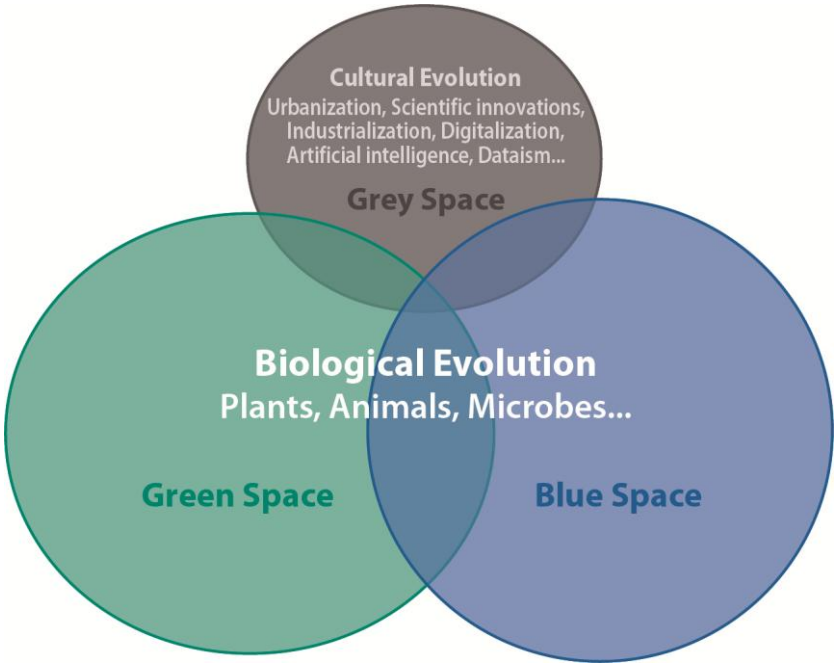
Accepted Article

Figure 5. The circle of causality. From the megatrend of urbanization to increase of non-communicable (inflammatory) diseases. Or the other way around, from symptoms to background factors.



This article is protected by copyright. All rights reserved.

Figure 6. Human kind has evolved from natural environments, i.e. from green (soil) and blue (waters) spaces, but is increasingly effected by cultural environment, i.e. gray (urban) space.



Accepted Article

This article is protected by copyright. All rights reserved.